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EDITORIAL COMMENT

Outcomes of PCSK9 Inhibitors

Does Sex Matter?*

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Despite significant advancements in medications targeting modifiable risk factors like hyperlipidemia, atherosclerotic cardiovascular disease (ASCVD) remains a significant cause of morbidity and mortality worldwide, affecting both women and men. Lowering low-density lipoprotein cholesterol (LDL-C) levels is a key aspect of ASCVD management. Studies have consistently shown a 22% relative risk reduction of major adverse cardiovascular events (MACE) for every 1 mmol/L reduction in LDL-C levels, whether achieved through statins or other lipid-lowering drugs.[1,2] Recent research has highlighted the potential benefits of achieving even lower LDL-C levels with PCSK9 inhibitors in additional reductions of cardiovascular events.[2,3] Consequently, multiple guidelines now recommend considering the addition of PCSK9 inhibitors to statin therapy for individuals at high risk of ASCVD.

The clinical approval of PCSK9 inhibitors for both primary and secondary prevention of ASCVD is attributed to their extraordinary efficacy in lowering lipid levels, their cardiovascular benefits, and their excellent safety profile. Through a meta-analysis of randomized trials, a significant reduction of 50 to 60% in plasma LDL-C levels was observed following PCSK9 inhibitors treatment.[4] This reduction was observed even in patients who were already receiving maximally tolerated statin therapy. Furthermore, a Bayesian network meta-analysis indicated that PCSK9 inhibitors may have a potential advantage over statins in terms of preventing MACE.[5]

While there is currently no solid evidence suggesting a significant attenuation of cardiovascular benefits from lipid-lowering therapy and other guideline-directed treatments in women compared to men, it is evident that women often experience disparities in cardiovascular care. Women are more frequently underdiagnosed, undertreated, and receive inadequate follow-up in clinical practice, which can contribute to higher in-hospital mortality rates for acute myocardial infarction among women.[6] In addition to these disparities, women may also face specific cardiovascular risk factors that are unique to their sex. Conditions such as pre-eclampsia, gestational hypertension, premature menopause, polycystic ovarian syndrome, fertility treatments, and autoimmune diseases can significantly increase the risk of future ASCVD in women. Therefore, it becomes crucial to investigate whether PCSK9 inhibitors, a class of drugs with proven efficacy to reduce ASCVD risk, are equally effective in women as they are in men. This investigation holds critical importance as it can guide clinical decisions regarding the prescription of PCSK9 inhibitors in women, ensuring equitable treatment and improved outcomes for female patients.

In this issue of *JACC: Advances*, Rivera et al[7] conducted a systematic review and meta-analysis to investigate potential sex differences in lipid and cardiovascular outcomes associated with PCSK9 inhibitors. The analysis included 16 studies with 54,996 patients. It is important to note that only 27.5% of the participants were females, indicating an underrepresentation of women in these trials. Among the studies analyzed, the 2 large cardiovascular outcomes trials, FOURIER and ODYSSEY OUTCOMES, included 27,564 and 18,924 participants, respectively. Both trials had a female percentage of approximately 25%. On the other hand, most of the smaller trials focused on

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lipid-lowering efficacy and had a higher percentage of women, with more than 40% representation.

In this meta-analysis, the use of PCSK9 inhibitors was associated with a significant reduction in LDL-C levels in both women and men. However, there was a statistically significant difference in the magnitude of LDL-C reduction between sexes. At 12 weeks, PCSK9 inhibitors were associated with a 62.6% reduction in LDL-C in women and a 66.2% reduction in men, with a mean difference of −4.6% ($P < 0.001$). This reduction was slightly attenuated but remained remarkable at 24 weeks, with a 47.5% reduction in women and a 54.1% reduction in men, and a mean difference of −7.1% ($P < 0.001$). These findings align with a sex-specific secondary analysis of the large FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, which also reported a greater reduction in LDL-C levels in men compared to women at 4 weeks.[8] However, the absolute change instead of percent change in LDL-C levels was reported in the secondary analysis at longer-term follow-up, and thus these data were not included in the present meta-analysis. More importantly, the meta-analysis demonstrated similar effectiveness of PCSK9 inhibitors in preventing MACE in both women and men, with approximately a 15% risk reduction observed in both sexes, and thus supports the use of PCSK9 inhibitors in both sexes.[7]

Interpreting the sex-specific differences related to PCSK9 inhibitors should be considered in the context of findings from other lipid-lowering agents. One collaborative meta-analysis involving 174,000 participants, including 47,000 women, demonstrated that statin therapy effectively reduces LDL-C levels by approximately 30% in both sexes. Additionally, the analysis found that the reduction in MACE per 1 mmol/L reduction in LDL-C was similar between women and men (16% vs 22% reduction, respectively), after adjusting for detailed cardiovascular risk factors.[9] Similarly, a secondary analysis of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which included 18,144 patients with 4,416 women, showed comparable absolute reductions in LDL-C (~16.4 vs 16.7 mg/dL reduction) and similar proportional reductions in MACE (12% vs 5%, respectively, with no significant difference) between women and men.[10] Therefore, a difference of lipid-lowering efficacy between sexes was observed in PCSK9 inhibitors, but not with statins and ezetimibe. This difference could potentially be attributed to variations in plasma PCSK9 levels between sexes. However, comparing outcomes across different classes of lipid-lowering agents can be challenging due to differences in study designs, factors adjusted for in analyses, among other factors.

Commendation should be given to the investigators for conducting a comprehensive and robust analysis of the available evidence on outcomes associated with PCSK9 inhibitors in women and men.[7] However, it is important to consider the potential limitations and exercise caution when interpreting the results. First, the meta-analysis did not account for baseline characteristic differences, other than sex, between women and men in individual trials. Therefore, it cannot conclusively determine the impact of sex on the efficacy and cardiovascular outcomes of PCSK9 inhibitors. The differences in LDL-C reduction observed between women and men could be influenced by non-sex-related differences in baseline characteristics within each group. It is plausible that women and men may have significant disparities in their baseline lipid profiles and cardiovascular risks. Second, the investigators did not evaluate the absolute risk reduction. While the relative risk reduction with PCSK9 inhibitors was similar for both sexes, it remains uncertain whether a comparable absolute risk reduction in MACE would be achieved. This uncertainty also arises from potential differences in baseline cardiovascular risks between women and men.

The ongoing debate regarding the effects of PCSK9 inhibitors between women and men highlights the need for further exploration. To enhance our understanding of sex differences in cardiovascular medicine and improve clinical decision-making, it is crucial to increase the representation of women in clinical trials and ensure consistent reporting of sex-specific efficacy and safety data, as recommended by the Institute of Medicine report.[11] Collaborative efforts and the utilization of individual participant data from these trials, similar to studies conducted on statins, would be instrumental in elucidating the influence of sex on LDL-C reduction and cardiovascular outcomes associated with PCSK9 inhibitors. Such collaborative initiatives would provide valuable insights into the differential treatment response based on sex, enabling more precise and tailored clinical management specific to each sex.

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